High Serum Selenium and Reduced Risk of Advanced Colorectal Adenoma in a Colorectal Cancer Early Detection Program

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Abstract

Background: **Epidemiologic and animal studies suggest that selenium may reduce risk of colorectal cancer. However, the epidemiologic data is mainly from relatively small investigations, limiting their interpretation. Although substantial evidence suggests that smoking is a strong effect modifier for other antioxidative nutrients, little is known about smoking-selenium interactions in colorectal tumors.**
Methods: **We studied the association of serum selenium and advanced colorectal adenoma, a cancer precursor, in 758 cases and 767 sex- and race-matched controls, randomly selected from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Cases had at least one verified advanced adenoma (≥1 cm or villous elements, or high-grade dysplasia) of the distal colon, and controls had a negative sigmoidoscopy.**
Results: **The multivariable odds ratio (OR) comparing participants in the highest quintile of serum selenium with those in the lowest quintile was 0.76 [95% confidence interval (95% CI), 0.53-1.10; P_{trend} = 0.01]. The inverse association between serum selenium and advanced colorectal adenoma was significant among recent smokers (OR, 0.53; 95% CI, 0.27-1.01 for highest versus lowest tertile; P_{trend} = 0.008). Serum selenium was unrelated to adenoma risk in nonsmokers and former smokers who quit smoking ≥10 years ago.**
Conclusion: **Selenium may reduce the risk of developing advanced colorectal adenoma, particularly among the high-risk group of recent smokers.** (Cancer Epidemiol Biomarkers Prev 2006;15(2):315–20)

Introduction

Colorectal cancer is the third most commonly diagnosed cancer in U.S. men and women, leading to >50,000 deaths annually (1, 2). Identifying modifiable risk factors is important for the prevention of this disease.

Interest in the essential trace element selenium as a colorectal cancer preventive agent was stimulated by the observation of a 61% reduction in colorectal cancer in the treatment arm of the Nutritional Prevention of Cancer Trial, a randomized placebo controlled trial for skin cancer prevention with selenium supplementation (200 μg selenium per day). This result is limited, however, in that colorectal cancer was not a primary end point of the trial, and the number of colorectal cancer cases was small (selenium arm = 8, placebo arm = 19).

Most observational studies investigating selenium exposure are small, because reliable data on selenium is largely restricted to selenium measures in biological tissues, due to large variations in the selenium content of foods resulting in imprecise dietary selenium intake estimates from questionnaires (3-5). The selenium levels of U.S. grains, dairy products, eggs, meat, poultry, and fish-all good sources of selenium-vary up to 10-fold, as a result of differences in the selenium concentration of the soil where the crops are grown (3-5), with high selenium soil content, for example, in Nebraska, the Dakotas, and Colorado, and lower content in the South and Northeast of the United States (6, 7). U.S. population intakes range between 50 and 250 μg/d (8-10), encompassing levels within the dosing level (200 μg/d) associated with colorectal cancer prevention in the Nutritional Prevention of Cancer Trial (11, 12).

A recent pooled analysis (13) of 1,012 cases of recurrent colorectal adenoma showed an inverse association between serum/plasma selenium and adenoma recurrence, with a preponderance of less advanced tumors. Pooled risk estimates indicate a stronger association for advanced adenoma; however, the power was limited (13). To examine associations between serum selenium and risk for advanced colorectal adenoma (i.e., tumors with a greater potential for malignant transformation), we studied more than 750 advanced colorectal adenoma cases and controls. Our interest was to explore interactions of selenium with tobacco use, because substantial evidence from animal and human studies, including randomized trials, suggests that smoking is a strong effect modifier for other antioxidative nutrients, including β-carotene and vitamin E (reviewed in ref. 14).

This case-control study was nested in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, in which colorectal adenoma were identified following a standard protocol in a large population characterized for colorectal cancer risk factors. Because the trial is conducted at 10 centers throughout the United States, it also captures the wide geographic differences in selenium intake in the U.S. population, which increase the power to detect an association (6, 7).

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Materials and Methods

This case-control study was nested within the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, which was designed to evaluate selected methods for the early detection of these cancers and to investigate etiologic factors and early markers of cancer (15, 16). Participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, ages 55 to 74 years, were recruited at 10 centers in the United States (Birmingham, AL; Denver, CO; Detroit, MI; Honolulu, HI; Marshfield, WI; Minneapolis, MN; Pittsburgh, PA; Salt Lake City, UT; St Louis, MO; and Washington, DC). Participants in the screening arm of the trial received sigmoidoscopic exam at baseline. If the sigmoidoscopy identified polyps or other suspect lesions, participants were advised to get further follow-up examination through their own medical care providers, which usually resulted in a full colonoscopy with polypectomy or surgical procedures, if indicated. All medical and pathologic reports of the follow-up examinations were obtained and coded by trained medical record abstractors. Written informed consent was obtained from participants, and the trial received approval from the institutional review boards of the U.S. National Cancer Institute and the 10 study centers.

Study Population. All cases and controls for this study were selected from 42,037 participants in the screening group who underwent a successful sigmoidoscopic examination at baseline (insertion to at least 50 cm with >90% of mucosa visible or a suspect lesion identified). Baseline sigmoidoscopy screening of selected cases and controls was conducted between September 1993 and September 1999. Participants provided information on risk factors and donated a blood sample for use in etiologic studies. After exclusion of 4,834 participants with a self-reported history of cancer (except basal cell skin cancer), ulcerative colitis, Crohn's disease, familial polyposis, colorectal polyps, or Gardner's syndrome, we randomly selected 772 cases for study from among 1,234 cases with advanced distal adenoma (adenoma ≥1 cm or containing villous elements or high-grade dysplasia). An equal number of sex- and race-matched participants (n = 777) with a negative screening sigmoidoscopy (i.e., no polyp or other suspect lesion; n = 26,651) were randomly selected as controls. Blood samples collected at study entry were available for selenium analysis from 759 cases and 767 controls.

Serum Selenium Analysis. Serum selenium concentrations were determined using inductively coupled plasma mass spectrometry (for details, see ref. 17). Equal numbers of cases and matched controls were analyzed in the same or consecutive batches. Quality control samples were monitored throughout the analysis. We excluded one case and one control due to extremely high serum selenium levels (>300 ng/mL). The within-batch repeatability coefficient of variation estimated from 182 duplicates was 5.5%, and the between-batch coefficient of variation estimated from 361 replicates was 7.4%.

Assessment of Questionnaire-Based Covariates. At initial screening, all participants were asked to complete a questionnaire about sociodemographic factors; medical history, including current and former use of hormone replacement therapy; and risk factors for cancer. Usual dietary intake over the 12 months before enrollment was assessed with a 137-item food frequency questionnaire, including an additional 14 questions about intake of vitamin and mineral supplements (18). Daily dietary nutrient intake was calculated by multiplying the daily frequency of each consumed food item by the nutrient value of the sex-specific portion size (19) using the nutrient database from the U.S. Department of Agriculture (20).

Statistical Analysis. Adjusted means (least-squares means) were calculated by linear models. To estimate the association between selenium and colorectal adenoma, we calculated odds ratios (OR) and 95% confidence intervals (95% CI) using unconditional logistic regression analysis, with selenium entered as a continuous variable or in quintiles, with cut points based on the selenium distribution in controls. We used the continuous variable to estimate for a linear trend. All Ps are two sided.

The ORs were adjusted for the matching factors, sex, and race, and in addition for age at randomization, study center, and year of blood draw. We evaluated confounding for known and potential risk factors of colorectal tumors, including physical activity, body mass index, smoking, alcohol intake, aspirin use, ibuprofen use, hormone replacement therapy (women only), family history of colorectal cancer, race, educational attainment, energy intake, red meat intake, folate intake, fiber intake, and calcium intake. None of the factors was included in the analyses because none of them changed the β coefficient of the risk estimates of selenium by >10%. Because the variation of the quality control samples in the last 16 batches was substantially larger than in the first 180 batches (SD = 24.5 and 8.4, respectively), we included an indicator variable for this batch effect [excluding participants analyzed in the last 16 batches (7.5% of all participants) did not change the association between selenium and adenoma risk].

Selenium levels are reported to be related to age, sex, smoking, and alcohol consumption (9, 10, 21, 22). Furthermore, other antioxidants, particularly vitamin E, may modify the effect of selenium (23, 24). To explore potential effect modification by age, sex, smoking, alcohol, and vitamin E, we did stratified analyses and evaluated multiplicative interaction by creating product terms, investigating the statistical significance of multiplicative interactions by comparison of the -2 log likelihood statistics of the main effect model with the joint effects model. For this analysis, we combined current smokers and those that quit smoking <10 years ago as recent smokers to avoid small cell numbers and to account for the relevant time period of advanced adenoma development. Former smokers were defined as those that quit smoking ≥10 years ago.

Results

The study population was mainly non-Hispanic White (94%) and male (70%). Controls were slightly younger than the advanced colorectal adenoma cases (average, 61.8 and 63.1 years, respectively). Mean serum selenium levels of the first and fifth quintile ranged from 108 to 174 ng/mL (Table 1). Those with high serum selenium levels were less likely to be female and tended to exercise more.

Adjusted mean serum selenium levels were significantly lower in cases (134.2 ± 23.3 ng/mL, mean ± SD) than controls (137.3 ± 23.3 ng/mL, mean ± SD; $P_{\text{difference}}$ = 0.007). Considering serum selenium as a continuous measure, risks for advanced adenoma were reduced by 26% for each 50 ng/mL increase in serum selenium (P_{trend} = 0.01), although the risk pattern was not clearly monotonic, when examined by quintile of selenium (Table 2). The inverse association was strongest in older participants (>67 years), showing a 52% reduction in advanced adenoma risk comparing those in the highest quintile with those in the lowest quintile (P_{trend} = 0.005; Table 2; $P_{\text{interaction}}$ = 0.09). In addition, men in the highest quintile of selenium had 43% lower risk for advanced colorectal adenoma compared with men in the lowest quintile of selenium (P_{trend} 0.001; Table 2), whereas serum selenium was unrelated to advanced adenoma risk in women ($P_{\text{interaction}}$ = 0.03). Within older participants (>67 years), we observed an inverse selenium-adenoma association for both men and women (data not

Table 1. Distribution of study characteristics by quintiles of serum selenium

	Quintiles				
	1	2	3	4	5
Selenium (mean, ng/mL)	108.2	123.8	134.1	144.8	173.8
Controls (n)	153	154	153	154	153
Age (mean, y)	62.3	61.4	61.8	61.3	62.3
Sex (%)	40.7	29.3	31.4	27.0	24.8
Race (%)					
Non-Hispanic Black	1.4	2.3	4.0	2.5	4.7
Non-Hispanic White	94.4	94.8	92.9	94.9	92.2
Others	4.2	2.9	3.1	2.6	3.1
Some college level education (%)	72.6	72.0	75.5	65.5	69.0
BMI (mean, kg/m^2)	27.5	27.7	27.5	27.4	27.2
Vigorous physical activity ≥ 1 h/wk (%)	22.7	28.0	31.0	30.2	34.7
Aspirin use >1 times/wk (%)	35.7	30.2	33.0	40.9	30.3
Ibuprofen use >1 times/wk (%)	12.9	13.0	14.8	17.7	14.0
Smoking status (%)					
Never	44.8	42.1	41.7	31.0	44.1
Former smokers*	37.2	37.9	38.2	44.2	36.0
Recent smokers†	11.1	15.4	14.8	17.5	13.3
Pipe and cigar (never cigarettes)	6.3	4.2	4.7	6.2	6.8
Alcohol ≥15 g/d (%)	26.3	22.1	27.9	27.2	26.7
Red meat intake (mean mg/d)	84.5	92.2	90.5	88.8	87.4
Fiber intake (mean g/d)	24.2	22.5	24.1	24.6	25.9
Calcium intake (mean mg/d)	1,256	1,215	1,304	1,296	1,222
Folate intake (mean μg/d)	597	597	621	654	620

NOTE: All values other than age, sex, and race were adjusted for age, sex, race, study center, batch effect, and year of blood draw; all values based on control participants only.
Abbreviation: BMI, body mass index.
*Former smokers = quit smoking ≥10 years ago.
†Recent smokers = current smokers or quit smoking <10 years ago.

shown), but numbers in these subgroups were small, resulting in wide confidence intervals.

Among recent smokers, defined as current smokers or those quit smoking <10 years ago, risks for colorectal adenoma were reduced 47% in the highest serum selenium tertile compared with the lowest tertile (P_{trend} = 0.008; Table 3; tertile grouping is used to avoid smaller stratum-specific numbers), with evidence for interaction of selenium and smoking in adenoma risk ($P_{\text{interaction}}$ = 0.03). This inverse association was even stronger when restricted to recent smokers that smoked >10 cigarettes per day (3rd versus 1st tertile: OR, 0.34; 95% CI, 0.16-0.72; P_{trend} = 0.0009). Smoking itself was a risk factor for advanced adenoma in this study population with strongest positive associations for recent smokers (OR, 2.61; 95% CI, 1.97-3.53 for recent smokers versus nonsmokers). The observed inverse association between serum selenium and advanced adenoma risk in recent smokers was present in men (3rd versus 1st tertile: OR, 0.51; 95% CI, 0.24-1.08; P_{trend} 0.02), in women (3rd versus 1st tertile: OR, 0.46; 95% CI, 0.09-2.31; P_{trend} 0.31), and in younger participants (≤67 years old; 3rd versus 1st tertile: OR, 0.48; 95% CI, 0.23-1.00; P_{trend} 0.02), although cell numbers, particular in women and older participants, were small. Among older participants, selenium was inversely associated with advanced colorectal adenoma risk in those who were former smokers (3rd versus 1st tertile: OR, 0.22; 95% CI, 0.07-0.70; P_{trend} = 0.01). Alcohol and vitamin E intake did not modify the association between serum selenium and adenoma risk (data not shown).

Discussion

We conducted a large study of 758 advanced colorectal adenoma cases and 767 sigmoidoscopy-negative controls, randomly selected from the same study population and screened for colorectal cancer with a standardized procedure. Overall, higher serum selenium levels were inversely associated with reduced risk of advanced colorectal adenoma. This inverse association between serum selenium and advanced adenoma risk was particularly strong in older persons and recent smokers.

In the Nutritional Prevention of Cancer Trial, 1,312 patients with a history of skin cancer were randomized to receive 200 μg selenium per day or placebo. Although the trial found no significant association between selenium supplementation and skin cancer recurrence (primary end point), significantly reduced risks were noted for overall cancer death and incidence of lung, prostate, and colorectal cancer (11). During the intervention period of up to 10 years (average, 4.5 years), 19 cases with colorectal cancer were diagnosed in the placebo group, whereas only eight cases were observed in the selenium group; a 61% risk reduction (95% CI, −10% to −83%; Table 4; ref. 11). Two additional years of follow-up with one more case in the placebo group add further support to this finding (25).

Three recent nested case-control studies of colorectal adenoma recurrence conducted within adenoma prevention

Table 2. Association between quintiles of serum selenium and risk of advanced distal colorectal adenomas: overall and stratified by age and sex

Selenium	Quintiles					P_{trend}	Per 50 ng/mL
	1*	2	3	4	5		
Quintile cut points (ng/mL)	<117.2	≥117.2-128.8	≥128.8-138.1	≥138.1-153.0	≥153.0		
Mean (ng/mL)	108.2	123.8	134.1	144.8	173.8		
Overall							
No. cases/controls	156/153	174/154	134/153	162/154	132/153		
OR (95% CI)†	1.00	1.14 (0.82-1.57)	0.93 (0.68-1.30)	1.10 (0.79-1.54)	0.76 (0.53-1.10)	0.01	0.74 (0.58-0.93)
Age ≤67 y							
No. cases/controls	110/125	128/134	104/125	125/129	97/119		
OR (95% CI)†	1.00	1.15 (0.80-1.65)	1.06 (0.72-1.54)	1.20 (0.82-1.75)	0.89 (0.59-1.36)	0.25	0.85 (0.64-1.14)
Age >67 y							
No. cases/controls	46/28	46/20	30/28	37/25	35/34		
OR (95% CI)†	1.00	1.41 (0.67-2.98)	0.67 (0.32-1.39)	0.88 (0.42-1.86)	0.48 (0.22-1.03)	0.005	0.49 (0.30-0.80)
Women							
No. cases/controls	52/66	64/48	43/49	47/43	22/29		
OR (95% CI)†	1.00	1.87 (1.07-3.28)	1.20 (0.66-2.15)	1.87 (1.02-3.43)	1.22 (0.59-2.52)	0.40	1.25 (0.75-2.09)
Men							
No. cases/controls	104/87	110/106	91/104	115/111	110/124		
OR (95% CI)†	1.00	0.82 (0.54-1.23)	0.75 (0.49-1.14)	0.79 (0.52-1.19)	0.57 (0.36-0.89)	0.001	0.63 (0.47-0.84)

*Reference category.
†Adjusted for age, sex, race, study center, batch effect, and year of blood draw.

Table 3. Association between tertiles of serum selenium and risk of advanced distal colorectal adenomas: stratified by smoking status

	Tertiles			P_{trend}	Per 50 ng/mL
	1*	2	3		
Tertile cut points (ng/mL)	<124.8	≥124.8-142.5	≥142.5		
Mean (ng/mL)	114.2	134.5	162.1		
Nonsmokers					
No. cases/controls	80/111	84/109	89/90		
OR (95% CI)†	1.00	1.25 (0.81-1.95)	1.27 (0.79-2.03)	0.82	0.95 (0.63-1.44)
Pipe or cigar					
No. cases/controls	12/11	11/10	16/22		
OR (95% CI)†	1.00	1.40 (0.29-6.78)	0.75 (0.20-2.84)	0.20	0.51 (0.18-1.43)
Former‡					
No. cases/controls	95/98	88/96	85/103		
OR (95% CI)†	1.00	0.92 (0.59-1.42)	0.84 (0.53-1.33)	0.23	0.79 (0.53-1.17)
Recent§					
No. cases/controls	80/33	58/39	57/39		
OR (95% CI)†	1.00	0.57 (0.30-1.06)	0.53 (0.27-1.01)	0.008	0.44 (0.24-0.81)

*Reference category.
†Adjusted for age, sex, race, study center, batch effect, and year of blood draw.
‡Former smoker = quit smoking ≥10 years ago.
§Recent smokers = current smokers or quit smoking <10 years ago.

trials also support a preventive role of selenium (13, 26). Studies, including 247 to 403 recurrent adenoma per study, showed 25% to 40% risk reductions for subjects with high serum selenium, and pooled analysis of all three studies resulted in a significant inverse association with a highly significant linear trend (Table 4; ref. 13). Most earlier studies of this topic have entailed relatively small numbers of cases, often with <100 cases (27-34). Several of these studies generally supported a role for selenium in colorectal cancer (27-30, 34-36) and adenoma prevention (27, 32, 33), although not all studies were statistically significant. Relatively few observational studies have reported either no association (29, 37), including the largest prospective study on colorectal cancer (37), or a nonsignificant positive association (31, 38). In agreement with our observations in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, several but mainly small observational studies and one

Table 4. Clinical trial and observational studies on selenium and colorectal tumors: ordered by study design and year of publication

First author, year, references	Cases	Outcome	Results (OR highest vs lowest quantile)	P_{trend}	Specimen
			OR (95% CI)		
Randomized trial					
Clark 1996 (11)	8/19*	CR	0.39 (0.17-0.90)	0.03	
Nested case-control studies and case-cohort studies					
Jacobs 2004 (13)	403	AR	0.67 (0.43-1.05)	0.21	Serum
	247	AR	0.66 (0.40-1.10)	0.13	Plasma
	362	AR	0.57 (0.34-0.95)	0.04	Serum
	Pooled	AR	0.66 (0.50-0.87)	0.006	Serum/plasma
Garland 1995 (31)	89	CR	2.04 (0.88-4.75)	0.12	Toenail
Van Brandt 1993 (37)	150†	C	1.07† (0.61-1.88)	0.55	Toenail
	76†	R	1.12† (0.49-2.55)	0.89	
Knekt 1990 (29)	32	CR, men	0.69	NS	Serum
	59	CR, women	1.26	NS	
Schober 1987 (30)	72	C	0.71		Serum
Nomura 1987 (35)	82	C	0.56	0.33	Serum
	32	R	0.63	0.66	
Case-control studies					
Fernandez-B. 2002 (27)	24	CR	Mean selenium levels lower in CR cases than controls (P = 0.006)		Serum
	28	A	In subjects ≤60 y: mean selenium levels lower in adenoma cases than controls (P = 0.002)		
Ghadirian 2000 (28)	92	CR	0.42 (0.19-0.93)	0.009	Toenail
Scieszka 1997 (34)	25	CR	Mean selenium levels lower in CR cases than controls (P = 0.002)		Plasma
Russo 1997 (33)	37	A	0.24 (0.06-1.04)	0.09	Plasma
Nelson 1995 (38)	139	A	1.8 (0.9-4.0)		Serum
	25	CR	1.7 (0.5-5.9)		
Clark 1993 (32)	24	A	0.24 (0.07-0.80)	0.04	Plasma
Zhao 1990 (36)	202	CR	Selenium levels lower in CR cases than controls (P = 0.01)		Blood

NOTE: Studies using dietary questionnaires to assess selenium intake or studies investigating gastrointestinal cancer only are not included.
Abbreviations: A, adenoma; AR, adenoma recurrence; C, colon cancer; CR, colorectal cancer; R, rectal cancer; NS, not significant.
*Number of colorectal cancer cases in selenium supplementation group/placebo group.
†Cases diagnosed during 1st year of follow-up were excluded. Results including all cases are for colon cancer (n = 216): OR, 0.79; 95% CI, 0.50-1.25; rectal cancer (n = 102): OR, 1.05; 95% CI, 0.57-1.94 for highest versus lowest quintile.

randomized trial found inverse associations between selenium and colorectal adenoma and cancer risk. Findings from our study and the pooled analysis (13) particularly support inverse association with advanced adenoma.

The inverse selenium-adenoma association in our study was limited to men, as was overall cancer incidence reduction in the Nutritional Prevention of Cancer Trial (results for colorectal cancer were not provided separately; refs. 11, 25). One observational study (29) also reported an inverse association in men only and another including only women found a positive association (31), but two studies reported inverse associations in both men and women (13, 28). Effect modification by gender may be due in part to gender differentials in selenium excretion rates (25, 39, 40), or to interactions with smoking, as observed in our study. Given the small percentage of women in our study and the Nutritional Prevention of Cancer Trial (refs. 11, 25; 30 and 25%, respectively), these gender differentials could also be attributed to chance; larger studies with sufficient numbers of women are needed to address this question (The Selenium and Vitamin E Cancer Prevention Trial, the largest ongoing randomized trial on selenium supplementation, includes men only as prostate cancer is the primary end point; ref. 41).

A large body of experimental data, including animal models for colon cancer (42-45), supports a role for selenium in cancer prevention (see for review, ref. 46), potentially acting through multiple pathways (47-49). Selenium, particularly methylated forms, directly affects cell cycle control and apoptosis (43, 50-52). In cell lines, selenomethionine activates p53, with related increases in p53-dependent DNA repair (53). Selenium may also interact with the folate/homocysteine pathway, potentially altering DNA methylation patterns (54-56), as an early step in colorectal cancer development (57).

Indirect effects of selenium in colorectal cancer prevention may be mediated through selenium-containing enzymes (such as glutathione peroxidase and selenoprotein P), particularly due to their antioxidative and anti-inflammatory properties (47, 58-61) in relation to food-derived oxidative stress (62, 63) and colorectal inflammation (64, 65).

The gastrointestinal tract expresses all four common glutathione peroxidases (*GPX1*, *GPX2*, *GPX3*, and *GPX4*), suggesting their importance in colonic function (62, 66). Targeted disruption of both cytosolic and gastrointestinal GPX genes (*GPX1* and *GPX2*, respectively) results in high susceptibility to inflammation and colon cancer in mice (49, 67). Oxidative stress, related to aging and smoking (both are risk factors for colorectal adenoma in this study population), could account for the strong inverse selenium-adenoma associations found in our study among older participants and recent smokers, possibly mediated through the antioxidative properties of selenoenzymes (68, 69). Our study is the first large study to explore interactions of selenium with smoking in colorectal tumors, and it will be interesting if future studies result in similar strong evidence for selenium-smoking interactions, as seen for other antioxidative nutrients (i.e., β-carotene and vitamin E; reviewed in ref. 14).

Mean serum selenium levels in the lowest and highest quintile in our study were 108 and 174 ng/mL, respectively, comparable with increase in serum selenium due to long-term supplementation in the Nutritional Prevention of Cancer Trial (with supplements mean serum selenium increased from 114 to 190 ng/mL; ref. 11). We observed the lowest serum selenium levels in Alabama and the District of Colombia and the highest levels in the Midwest (Michigan, Wisconsin, and Minnesota); however, this pattern was only in part consistent with local soil selenium levels reported for the United States (6, 7), probably due to nationwide food distribution of foods high in selenium.

The wide range of selenium levels in our study and the relatively large sample size increased the power to detect significant selenium-adenoma associations, overall, and to conduct stratified analysis. Findings were unlikely affected by prior screening, as results were similar when stratified by conduct of previous endoscopy or fecal occult blood test (data not shown). Advantages of conducting the study in a screening trial were that cases and sigmoidoscopy-negative controls were selected from the same source population of largely asymptomatic individuals and were screened with a standardized procedure, avoiding many of the biases of studies carried out in adenoma cases identified due to symptoms or signs of colorectal cancer.

In summary, higher serum selenium levels were associated with reduced risk of advanced colorectal adenoma, which seems more prominent in recent smokers. Because oxidative stress is related to smoking, the observed interactions with selenium may be mediated through the antioxidative properties of selenoenzymes.

References

1. National Cancer Institute. SEER Cancer Statistics Review 1975 – 2001. August 2004. Available from: http://seer.cancer.gov/csr/1975_2001/sections.html.
2. U.S. Cancer Statistics Working Group. United States cancer statistics: 2000 incidence. Atlanta (GA): Department of Health and Human Services, Center for Disease Control and Prevention and National Cancer Institute; 2004.
3. Finley J, Matthys L, Shuler T, Kotynta E. Selenium content of foods purchased in North Dakota. Nutr Res 1996;16:865 – 71.
4. Levander OA. Considerations on the assessment of selenium status. Fed Proc 1985;44:2579 – 83.
5. Holden J, Gebhardt R, Davis C, Lurie D. A nationwide study of the selenium content and variability in white bread. J Food Comp Anal 1991;4:183 – 95.
6. Grossman JN, Grosz AE, Schweitzer PN, Schruben PN; The National Geochemical Survey Team. The National Geochemical Survey: database and documentation. U.S. Geological Survey Open-File Report 2004 – 1001. Available from: http://tin.er.usgs.gov/geochem/doc/averages/se/usa.html. 2005.
7. Kubota J, Allaway WH, Carter DL, et al. Selenium in crops in the United States in relation to selenium-responsive diseases of animals. J Agric Food Chem 1967;15:448.
8. Longnecker MP, Taylor PR, Levander OA, et al. Selenium in diet, blood, and toenails in relation to human health in a seleniferous area. Am J Clin Nutr 1991;53:1288 – 94.
9. Hunter DJ, Morris JS, Chute CG, et al. Predictors of selenium concentration in human toenails. Am J Epidemiol 1990;132:114 – 22.
10. Panel on Dietary Antioxidants and Related Components. Dietary reference intakes for vitamin C, vitamin E, selenium and beta-carotene and other carotenoids. Washington (DC): National Academy Press; 2000.
11. Clark LC, Combs GF, Jr., Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. JAMA 1996;276:1957 – 63.
12. Clark LC, Dalkin B, Krongrad A, et al. Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. Br J Urol 1998;81:730 – 4.
13. Jacobs ET, Jiang R, Alberts DS, et al. Selenium and colorectal adenoma: results of a pooled analysis. J Natl Cancer Inst 2004;96:1669 – 75.
14. Mayne ST, Lippman SM. Cigarettes: a smoking gun in cancer chemoprevention. J Natl Cancer Inst 2005;97:1319 – 21.
15. Gohagan JK, Prorok PC, Hayes RB, Kramer BS. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial of the National Cancer Institute: history, organization, and status. Control Clin Trials 2000; 21:251 – 72S.
16. Hayes RB, Reding D, Kopp W, et al. Etiologic and early marker studies in the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial. Control Clin Trials 2000;21:349 – 55S.
17. Stürup S, Hayes RB, Peters U. Development and application of a simple routine method for the determination of selenium in serum by octopole reaction system ICPMS. Anal Bioanal Chem 2005;381:686 – 94.
18. Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. 2003 [cited 2003 May]. Available from: http://www3.cancer.gov/prevention/plco/DQX.pdf.
19. Subar AF, Midthune D, Kulldorff M, et al. Evaluation of alternative approaches to assign nutrient values to food groups in food frequency questionnaires. Am J Epidemiol 2000;152:279 – 86.
20. Tippett KS, Cypel YS. Design and operation: the continuing survey of food intakes by individuals and the Diet and Health Knowledge Survey, 1994 – 96. In: Continuing survey of food intakes by individuals 1994 – 96, Nationwide Food Surveys Rep. No. 96 – 1. U.S. Department of Agriculture, Agricultural Research Service; 1997.
21. Lloyd B, Lloyd RS, Clayton BE. Effect of smoking, alcohol, and other factors on the selenium status of a healthy population. J Epidemiol Community Health 1983;37:213 – 7.

22. Swanson CA, Longnecker MP, Veillon C, et al. Selenium intake, age, gender, and smoking in relation to indices of selenium status of adults residing in a seleniferous area. Am J Clin Nutr 1990;52:858–62.
23. Helzlsouer KJ, Huang HY, Alberg AJ, et al. Association between alpha-tocopherol, gamma-tocopherol, selenium, and subsequent prostate cancer. J Natl Cancer Inst 2000;92:2018–23.
24. Willett WC, Polk BF, Morris JS, et al. Prediagnostic serum selenium and risk of cancer. Lancet 1983;2:130–4.
25. Duffield-Lillico AJ, Reid ME, Turnbull BW, et al. Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the Nutritional Prevention of Cancer Trial. Cancer Epidemiol Biomarkers Prev 2002;11:630–9.
26. Wallace K, Byers T, Morris JS, et al. Prediagnostic serum selenium concentration and the risk of recurrent colorectal adenoma: a nested case-control study. Cancer Epidemiol Biomarkers Prev 2003;12:464–7.
27. Fernandez-Banares F, Cabre E, Esteve M, et al. Serum selenium and risk of large size colorectal adenomas in a geographical area with a low selenium status. Am J Gastroenterol 2002;97:2103–8.
28. Ghadirian P, Maisonneuve P, Perret C, et al. A case-control study of toenail selenium and cancer of the breast, colon, and prostate. Cancer Detect Prev 2000;24:305–13.
29. Knekt P, Aromaa A, Maatela J, et al. Serum selenium and subsequent risk of cancer among Finnish men and women. J Natl Cancer Inst 1990;82:864–8.
30. Schober SE, Comstock GW, Helsing KJ, et al. Serologic precursors of cancer. I. Prediagnostic serum nutrients and colon cancer risk. Am J Epidemiol 1987; 126:1033–41.
31. Garland M, Morris JS, Stampfer MJ, et al. Prospective study of toenail selenium levels and cancer among women. J Natl Cancer Inst 1995;87: 497–505.
32. Clark LC, Hixson LJ, Combs GF, Jr., Reid ME, Turnbull BW, Sampliner RE. Plasma selenium concentration predicts the prevalence of colorectal adenomatous polyps. Cancer Epidemiol Biomarkers Prev 1993;2:41–6.
33. Russo MW, Murray SC, Wurzelmann JI, Woosley JT, Sandler RS. Plasma selenium levels and the risk of colorectal adenomas. Nutr Cancer 1997;28: 125–9.
34. Scieszka M, Danch A, Machalski M, Drozdz M. Plasma selenium concentration in patients with stomach and colon cancer in the Upper Silesia. Neoplasma 1997;44:395–7.
35. Nomura A, Heilbrun LK, Morris JS, Stemmermann GN. Serum selenium and the risk of cancer, by specific sites: case-control analysis of prospective data. J Natl Cancer Inst 1987;79:103–8.
36. Zhao N. [A case-control study of risk factors of colorectal cancer in Shanxi Province]. Zhonghua Liu Xing Bing Xue Za Zhi 1990;11:295–8.
37. Van den Brandt PA, Goldbohm RA, van't Veer P, et al. A prospective cohort study on toenail selenium levels and risk of gastrointestinal cancer. J Natl Cancer Inst 1993;85:224–9.
38. Nelson RL, Davis FG, Sutter E, et al. Serum selenium and colonic neoplastic risk. Dis Colon Rectum 1995;38:1306–10.
39. Rodriguez Rodriguez EM, Sanz Alaejos MT, Diaz RC. Urinary selenium status of healthy people. Eur J Clin Chem Clin Biochem 1995;33:127–33.
40. Waters DJ, Chiang EC, Cooley DM, Morris JS. Making sense of sex and supplements: differences in the anticarcinogenic effects of selenium in men and women. Mutat Res 2004;551:91–107.
41. Klein EA, Thompson IM, Lippman SM, et al. SELECT: the next prostate cancer prevention trial. Selenum and Vitamin E Cancer Prevention Trial. J Urol 2001;166:1311–5.
42. Baines AT, Holubec H, Basye JL, et al. The effects of dietary selenomethionine on polyamines and azoxymethane-induced aberrant crypts. Cancer Lett 2000;160:193–8.
43. Finley JW, Davis CD, Feng Y. Selenium from high selenium broccoli protects rats from colon cancer. J Nutr 2000;130:2384–9.
44. Rao CV, Wang CQ, Simi B, et al. Chemoprevention of colon cancer by a glutathione conjugate of 1,4-phenylenebis(methylene)selenocyanate, a novel organoselenium compound with low toxicity. Cancer Res 2001;61:3647–52.
45. Reddy BS, Wynn TT, El Bayoumy K, Upadhyaya P, Fiala E, Rao CV. Evaluation of organoselenium compounds for potential chemopreventive properties in colon cancer. Anticancer Res 1996;16:1123–7.
46. Combs GF, Jr., Gray WP. Chemopreventive agents: selenium. Pharmacol Ther 1998;79:179–92.
47. Rayman MP. The importance of selenium to human health. Lancet 2000;356: 233–41.
48. Duffield-Lillico AJ, Shureiqi I, Lippman SM. Can selenium prevent colorectal cancer? A signpost from epidemiology. J Natl Cancer Inst 2004;96: 1645–7.
49. Chu FF, Esworthy RS, Doroshow JH. Role of Se-dependent glutathione peroxidases in gastrointestinal inflammation and cancer. Free Radic Biol Med 2004;36:1481–95.
50. Ip C, Thompson HJ, Zhu Z, Ganther HE. *In vitro* and *in vivo* studies of methylseleninic acid: evidence that a monomethylated selenium metabolite is critical for cancer chemoprevention. Cancer Res 2000;60:2882–6.
51. Ip C, Dong Y. Methylselenocysteine modulates proliferation and apoptosis biomarkers in premalignant lesions of the rat mammary gland. Anticancer Res 2001;21:863–7.
52. Vadhanavikit S, Ip C, Ganther HE. Metabolites of sodium selenite and methylated selenium compounds administered at cancer chemoprevention levels in the rat. Xenobiotica 1993;23:731–45.
53. Seo YR, Kelley MR, Smith ML. Selenomethionine regulation of p53 by a ref1-dependent redox mechanism. Proc Natl Acad Sci U S A 2002;99: 14548–53.
54. Davis CD, Uthus EO. Dietary folate and selenium affect dimethylhydrazine-induced aberrant crypt formation, global DNA methylation and one-carbon metabolism in rats. J Nutr 2003;133:2907–14.
55. Gonzalez S, Huerta JM, Alvarez-Uria J, Fernandez S, Patterson AM, Lasheras C. Serum selenium is associated with plasma homocysteine concentrations in elderly humans. J Nutr 2004;134:1736–40.
56. Uthus EO, Yokoi K, Davis CD. Selenium deficiency in Fisher-344 rats decreases plasma and tissue homocysteine concentrations and alters plasma homocysteine and cysteine redox status. J Nutr 2002;132:1122–8.
57. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990;61:759–67.
58. Jozanov-Stankov O, Demajo M, Djujic I, Mandic M. Selenium intake as a modulator of responsiveness to oxidative stress. J Environ Pathol Toxicol Oncol 1998;17:251–7.
59. Rao L, Puschner B, Prolla TA. Gene expression profiling of low selenium status in the mouse intestine: transcriptional activation of genes linked to DNA damage, cell cycle control and oxidative stress. J Nutr 2001;131: 3175–81.
60. Spallholz JE, Boylan LM, Larsen HS. Advances in understanding selenium's role in the immune system. Ann N Y Acad Sci 1990;587:123–39.
61. Baines A, Taylor-Parker M, Goulet AC, Renaud C, Gerner EW, Nelson MA. Selenomethionine inhibits growth and suppresses cyclooxygenase-2 (COX-2) protein expression in human colon cancer cell lines. Cancer Biol Ther 2002;1:370–4.
62. Tham DM, Whitin JC, Kim KK, Zhu SX, Cohen HJ. Expression of extracellular glutathione peroxidase in human and mouse gastrointestinal tract. Am J Physiol 1998;275:G1463–71.
63. Sanders LM, Henderson CE, Hong MY, et al. Pro-oxidant environment of the colon compared to the small intestine may contribute to greater cancer susceptibility. Cancer Lett 2004;208:155–61.
64. Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. Am J Physiol Gastrointest Liver Physiol 2004;287:G7–17.
65. Clevers H. At the crossroads of inflammation and cancer. Cell 2004;118: 671–4.
66. Mork H, Lex B, Scheurlen M, et al. Expression pattern of gastrointestinal selenoproteins: targets for selenium supplementation. Nutr Cancer 1998;32: 64–70.
67. Chu FF, Esworthy RS, Chu PG, et al. Bacteria-induced intestinal cancer in mice with disrupted Gpx1 and Gpx2 genes. Cancer Res 2004;64:962–8.
68. Loft S, Poulsen HE. Cancer risk and oxidative DNA damage in man. J Mol Med 1996;74:297–312.
69. Frei B, Forte TM, Ames BN, Cross CE. Gas phase oxidants of cigarette smoke induce lipid peroxidation and changes in lipoprotein properties in human blood plasma. Protective effects of ascorbic acid. Biochem J 1991;277:133–8.